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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCGAW, MICHAEL M	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,609	SMITH ET AL.	
	Examiner	Art Unit	
	Michael M. McGaw	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☒ Claim(s) *2,8,9,14,16,18,24,26,27 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *Oct 14, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to applicant's communication filed on August 24, 2004. Claims 1-29 are currently pending and under examination.

Response to Amendment

It is noted that the specification has been amended to properly reflect the filing year of provisional application number 60/433,058.

Drawings

The drawings were received on August 24, 2004. These drawings are acceptable.

Claim Objections

The following claims are objected to for reasons outlined below: 2, 8, 9, 14, 16, 18, 24, 26, 27 and 29.

Numerous problems exist with the dependencies of the claims. Applicant is strongly encouraged to check claim dependencies to ensure that the claims properly refer to that from which it is intended.

Claim 2 objected to because of the following informalities: Claim 2 contains text that appears to be extraneous. The text refers to "the at least one helper function in the host cell of step (a) $5x10^7$ to $5x10^8$ per mL. is encoded..." It appears that "$5x10^7$ to $5x10^8$ per mL." does not belong in the claims. Appropriate correction is required.

Claims 8 and 9 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim because a claim must refer back to and further limit another claim or claims. See MPEP § 608.01(n). Claim 8 is

dependent on claim 8. Claim 9 is dependent on claim 9. Claim 8 is being treated as being dependent on claim 7. Claim 9 is being treated as being dependent on claim 8. Such treatment does not relieve applicant of response. Appropriate correction is required.

Claims 9 and 26 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Note that the concentration range is identical in claims 8, 9, and 26. Claims 8, 9 and 26 are directed at specifying the concentration of an electroporation mixture. Claim 8 refers to "[t]he method of claim 8..." Claim 9 refers to "[t]he method of claim 9..." Claim 26 refers to the method of claim 9. With the exception of the dependencies of the preamble the text of these claims is identical. Consequently, claims 9 and 26 fail to further limit the claims from which they depend.

Applicant is advised that should claim 24 be found allowable, claim 27 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The text of claims 24 and 27 is identical. Both claims state: "The method of claim 17, wherein the alphavirus is Venezuelan equine encephalitis virus (VEE)."

Claim 14 specifies an electroporation ratio between an (1) alphavirus replicon RNA (2) a first helper RNA molecule and (3) a second RNA helper molecule. It appears that applicant seeks to specify a range for the mixture and has provided a lower boundary for the ratio of 1:0.3:0:0.3. Applicant has specified four parameters for the range. Does applicant mean to have only three parameters such as 1:0.3:0.3 (where the relative concentration is (1) alphavirus replicon RNA (2) a first helper RNA molecule and (3) a second RNA helper molecule, respectively)?

Claim 16 refers to the method of claim 15, but is not within the range of values specified within claim 15. Does applicant mean to refer to the method of claim 14?

Claim 18 is directed at defining electroporation conditions and refers to the method of claim 11. Claim 11 does not involve electroporation at all, but claim 17 is directed at electroporation. It appears that applicant meant to refer to the method of claim 17, rather than claim 11. In the interest of compact prosecution the claim will be interpreted as referring to claim 17. Such treatment does not relieve applicant of response to the rejection.

Claim 29 states: "An alphavirus replicon particle preparation prepared by the method of ***any of*** claim 1." (emphasis added) It is not clear what is meant by any of claim 1. This claim is being interpreted as "An alphavirus replicon particle preparation prepared by the method of claim 1." Such treatment does not relieve applicant of response to the rejection.

Appropriate correction of all of the aforementioned claim objections is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 24 and 27 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Pushko, P. et al. (1997).

Applicant claims "A method of preparing alphavirus replicon particles comprising introducing an alphavirus replicon vector and one or more helper nucleic acid molecules into alphavirus-permissive cells via electroporation, wherein concentration of the alphavirus permissive cells in culture medium during electroporation is from $5x10^7$ to $5x10^8$ cells/mL and wherein the concentration of the alphavirus RNA replicon vector added to the cells prior to electroporation is approximately 35 μg per mL."

Pushko, P. et al. teaches methods of preparing alphavirus replicon particles comprising introducing an alphavirus replicon vector and one or more helper nucleic acid molecules into alphavirus-permissive cells via electroporation. Pushko's vector was based upon an attenuated strain of VEE. Pushko does not

disclose a specific concentration range of the alphavirus permissive cells in culture medium during electroporation nor does he disclose the concentration of the alphavirus RNA replicon vector. Nevertheless, both were present in the electroporation mixture at an efficacious concentration. Additionally, as outlined more fully below, one would know that such concentrations can be optimized. See also Liljestrom, P. et. al. (1991) J. Virol. 65:4107-4113. Pushko is discussed more fully immediately below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-12, 14-27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pushko, P. et al. (1997) in view of Bell, J. W. et. al. (1978).

Applicant claims "[a] method for preparing alphaviral replicon particles (ARPs), comprising the steps of:

(a) introducing an alphavirus replicon nucleic acid into a host cell, said replicon nucleic acid comprising at least a virus packaging signal and at least one heterologous coding sequence expressible in said alphaviral replicon nucleic

acid, wherein said host cell comprises at least one helper function, to produce a modified host cell;

(b) culturing said modified host cell under conditions allowing expression of the at least one helper function, allowing replication of said alphaviral replicon nucleic acid and packaging of said alphaviral replicon nucleic acid to form ARPS;

(c) contacting the modified host cells after step (b) with an aqueous solution having an ionic strength of from 0.2 M to 5 M to release the ARPS into the aqueous solution to produce a ARP-containing solution;

(d) collecting ARPS from the ARP-containing solution of step (c).

Pushko, P. et al. (1997) Virology 239: 389-401 teach a replicon vaccine vector system based on an attenuated strain of VEE. (see abstract) The replicon nucleic acid consisted of cis-acting 5' and 3' ends of the VEE genome, the complete nonstructural protein gene region, and the subgenomic 26S promoter. The VEE structural protein genes were replaced with either influenza hemagglutinin (HA) or Lassa virus nucleocapsid (N) genes (i.e. heterologus coding sequence). Pushko reports that these replicon RNAs directed the efficient, high-level synthesis of the HA or N proteins. For packaging of replicon RNAs into VEE replicon particles, the VEE capsid and glycoproteins were supplied in trans by expression from helper RNAs coelectroporated with the replicon. While both the replicon and the helper RNA retain the cis-acting terminal sequences required for genome replication and promoter transcription of the subgenomic mRNA, only the replicon retained the packaging signal(s). (see

page 390, col. 1) The replicon RNA is then packaged into replicon particles by the viral structural proteins supplied in trans.

Thus, Pushko teaches introducing an alphavirus replicon nucleic acid into a host cell, where the replicon nucleic acid comprises at least a virus packaging signal and at least one heterologous coding sequence expressible in the alphaviral replicon nucleic acid, where the host cell comprises at least one helper function, to produce a modified host cell. In this case the helper functions were provided by either monopartite or bipartitie helper systems. (see page 391, col. 1 and page 393, fig. 1). Pushko teaches culturing the modified host cell under conditions allowing expression of the at least one helper function, allowing replication of the alphaviral replicon nucleic acid and packaging of the alphaviral replicon nucleic acid to form ARPS. (see page 395, col. 2) Pushko does not teach the effect of salt concentration on the modified host cell after the culturing step to release the ARPS into the aqueous solution to produce a ARP-containing solution.

Bell, J. W. et. al. (1978) Journal of Virology, vol. 25(3), pp. 764-769 teaches the effect of salt concentration on the release of alphavirus particles in cell culture systems. Bell describes results from cell culture systems used to replicate Sindbis virus. Bell reports that when NaCl concentration is lowered maturation of infectious particles and particle release is significantly reduced. (see page 764, col. 1) The importance of Bell is that it establishes a dependence between NaCl concentration and particle release at the point when particles are harvested in cell culture. While Bell does not explicitly teach an optimal salt

concentration or range, one would recognize from Bell's disclosure that one should optimize the NaCl concentration because such optimization greatly affects virus particle yield. See MPEP 2144.05:

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)

One of ordinary skill in the art would have been motivated to combine the teachings of Pushko and Bell because Pushko teaches a variety of techniques for generation of replicon particles including the bipartite system where the generation of infectious particles is greatly diminished while Bell teaches increased yields of alphavirus particles by increasing the salt concentration at the point of harvest. One of ordinary skill in the art would have expected an increased yield of non-infectious particles because the techniques were well-established at the time of applicant's invention. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Pushko discloses the use of Vero cells as the alpha-virus permissible cells. (see page 390) As to the ratio of the various molecules, the gap between the electrode, the concentration of the helper, as variously expressed in claims 14-18 and 20, Pushko does not disclose the exact conditions of the electroporation. Nevertheless, one would recognize the value of optimizing the

mix and the gap between the electrodes to ensure transfection of 100% of the cells through routine experimentation. As to claims 10 and 12, one would reasonably wash the cells and would perform this wash in a medium of reduced salt to prevent premature release of virus. One would also use deoxyribonuclease to remove residual nucleic acid in the media. As to claim 5, this again appears to be a matter of routine optimization/experimentation. As to claim 22, one would reasonably filter or purify the virus following harvest.

As to claims 13 and 28, Pushko used the RiboMAX T7 RNA polymerase to produce transcripts and indicates that the transcripts were capped. (page 391, col. 1) Technical Bulletin No. 166 for the RiboMAX Large Scale RNA Production System from Promega indicates on page 6 that "some capped transcripts may demonstrate increased efficiency", but it does not indicate that cap analog is a requirement. Applicant indicates that others in the field have made similar observations when working with replicon systems. (see page 27 of the specification). Again, the use of capped vs. uncapped transcripts would appear to be within the purview of routine experimentation.

Claims 2, are rejected under 35 U.S.C. 103(a) as being unpatentable over over Pushko, P. et al. (1997) in view of Bell, J. W. et. al. (1978) as applied to claims 1 and 3-29 above, and further in view of Polo, J.M. et. al. (1999).

Claim 2 specifies that the at least one helper function in the host cell is encoded by a nucleic acid sequence stably integrated within the genome of the host cell. Pushko, P. et al. (1997) in view of Bell, J. W. et. al. (1978) does not

teach the at least one helper function in the host cell is encoded by a nucleic acid sequence stably integrated within the genome of the host cell but Polo, J.M. et. al. (1999) teaches such a cell.

Polo, J.M. et. al. (1999) Proc. Natl. Acad. Sci. vol. 96, pp. 4598-4603 describes the production of stable alphavirus packaging cell lines for Sindbis virus and Semliki forest virus-derived vectors. Polo teaches that these stable cell lines overcome the limitations of RNA-based vector replicon systems including the limitiations for large-scale preparations associated with the fact that vector replicons are suicide vectors, incapable of packaging progeny vector particles and causing productive infection, and the limitation associated with the generation of contaminating replication-competent virus. (see page 4598, col. 2) Such a teaching would provide the motivation to apply Polo's teaching to the teachings of Pushko, P. et al. (1997) in view of Bell, J. W. et. al. (1978). One of ordinary skill in the art would have expected an increased yield of non-infectious particles because the techniques were well-established at the time of applicant's invention. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Liljestrom, P. et. al. (1991) J. Virol. 65:4107-4113 describe electroporation to introduce RNA into cells where the transfection efficiency was greatly

enhanced over other methods. Liljestrom was working with infectious SFV RNA and BHK cells. Most critically, Liljestrom teaches the importance of optimizing transfection efficiency to ensure that 100% of the cells are transfected. (see page 4109, col. 1)

W/O 99/07834 to Cantab Pharmaceuticals teaches recovery of virus from cell culture using a hypertonic solution. W/O 99/07834 was directed most specifically at the harvest of herpesvirus from Vero cells, but the methods would generally be applicable to other enveloped viruses. W/O 99/07834 teaches harvesting in a variety of hypertonic salt solutions. (see page 3, line 12) W/O 99/07834 teaches that the harvested liquid should be filtered. (see page 4, line 8; page 6). W/O 99/07834 teaches washing of cells. W/O 99/07834 teaches the treatment of cells with nuclease enzyme to degrade free nucleic acid. (page 4, line 20)

Rayner, J.O. et. Al. (2002) Rev. Med. Virol. 12:279-296 describes a variety of alphavirus vector systems based upon SIN, SFV and VEE viruses.

Bredenbeek, P.J. et. al. (1993) J. Virol. 67(11) pp. 6439-6446, teaches the packaging of RNA replicons using defective helper RNA. Among other things, Bredenbeek indicates the importance of transfection efficiency when using replicon systems. (see p. 6439, col. 2 and p. 6444, col. 2). Bredenbeek indicates the use of the 5' cap analog in the transcription reaction. (see p. 6440, col. 1)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number

is (571) 272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

M.M.

Thursday, November 04, 2004

JAMES HOUSEL 11/5/04
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